NOTES ON POISONS.

NOTES FROM KOLLIKER'S "PHYSIOLOGICAL RESEARCHES ON THE ACTION OF SOME POISONS" PUBLISHED IN VIRCHOW'S ARCHIV. &c. VOL. X., 1856.

As we hope at some future period to return to the consideration of these very valuable researches, we shall do no more at present than state that many of the experiments are of a novel character, and that as a whole they constitute the most remarkable contribution to the knowledge of the physiological action of poisons which has been published in recent times. The ingenuity with which they have been designed, and the dexterity of their execution are entirely worthy of their distinguished author; and they promise not merely to add some new facts of importance, but to introduce into our knowledge of the subject, and the methods of its experimental investigation, an amount of precision far greater than has previously existed. The majority of the experiments were performed on frogs, but a number were also made on rabbits, and a few on dogs.

1. WOORARA, (URARI.)

The following is the statement of the general results deduced from fifty-three experiments made with woorara poison (p. 71):—

1. Woorara kills very rapidly from the blood and from wounds; but slowly, and, especially in mammalia, only in large doses from the alimentary mucous membrane. From the skin, it is inactive in frogs.

2. Frogs completely poisoned by small doses of woorara, and with nerves quite paralysed, may gradually recover themselves; and so also may mammiferous animals, when poisoned by large doses, if artificial respiration be kept up.

3. Woorara paralyses through the blood the motor nerves of the voluntary muscles; in a few minutes in frogs the ends of the nerves in the muscles, and in 1 to 2 hours the nervous trunks. If after the occurrence of the paralysis of the nervous extremities, the heart be excised, so as to prevent the nervous trunks from receiving a greater quantity of the poison than the ends the trunks become paralysed in 3 to 4 hours.

4. The brain is less affected than the nerves in the muscles; yet in partial poisoning, the voluntary motions soon disappear, while there remain spontaneous motions of a doubtful nature for a half or whole hour after the poisoning has commenced, which probably proceed from the medulla oblongata.

5. The spinal marrow is considerably less affected than the brain by the arrow poison, and as is shown by partial poisonings, preserves its reflex power for ½ to 1½ hours, and the irritability of its white substance, even 2 and 3 hours after the poisoning begins. It is also worthy of remark, that in such cases the lowered reflex power may be again re-excited by the direct application of strychnine to the medulla.

6. The sensory nerves remain active in partial poisonings, so long as reflex actions can be perceived, and when the action is restored by strychnine, show themselves not in the least affected, so that it appears doubtful whether the woorara has any action on the sensitive nerves.

7. The nerves of the involuntary muscles and of the glands appear also to be paralysed by woorara; at least this is true as to the vagus in its action on the

heart, the sympathetic in its relation to the iris, the nerves of the posterior lymphatic hearts, the vaso-motor nerves of the web of the frog's foot, the splanchnici in their action upon the peristaltic motion, and the nerves influencing the secretion of the submaxillary gland.

8. The voluntary muscles retain in poisoning by woorara their full irritability, but show a greater tendency to merely local contractions. In general, the rigor mortis appears later in these muscles than usual.

9. The non-striated muscles also remain irritable long after poisoning by woorara.

10. The heart in amphibia is little affected by woorara, and its contractions and the circulation continue regularly many hours after poisoning. It is only to be remarked, that the number of the heart's beats is somewhat increased, in consequence of the paralysis of the vagi. Hearts which have been divided in a poisoned frog, show the same phenomena as in one not poisoned, viz., that the part containing the ganglia continues to contract, while the other ceases, which leads to the conclusion that these ganglia are not paralysed. As regards the nerves within the heart, indubitably the ramifications of the vagus are paralysed, and it is not improbable that the sympathetic ramifications, as also the fibres arising from its ganglia, are similarly affected.

11. The lymphatic hearts of the frog remain still contractile for a short time after woorara poisoning.

12. The blood of animals poisoned with woorara, is fluid and dark; yet it coagulates readily when out of the vessels, and forms a soft coagulum, which only reddens slightly in the air. Woorara mixed directly with blood does not hinder its coagulation; but the blood is dark and scarcely reddens in the air.

14. Woorara solutions, when more concentrated, paralyse the nerves when locally applied; but yet, only very slowly, and they appear also to act upon the nerves within the muscles. Dilute solutions, on the contrary, have no hurtful effect. Applied to the brain and spinal marrow directly, woorara is quite innocuous when absorption is prevented.

15. When in mammalia, poisoned by woorara, the circulation is well maintained by artificial respiration, a number of secretions are more or less obviously increased (Bernard, Kölliker), an effect which may be due to the paralysis of the nerves, and the consequent dilatation of the vessels.

16. In mammalia, death from woorara is the effect of the paralysis of the respiratory nerves, and the consequent cessation of the respiration, which in these animals causes convulsions as an after concomitant effect. In frogs, the ultimate cessation of the functions is also perhaps the effect of the suspension of respiration, and of the defective oxidation of the blood, which render the heart incapable of further action; but in these animals, the cause of death is by no means so clear, from the functions being in a great degree independent of the respiration.

As an illustration of the manner in which these very remarkable and conclusive experiments were performed, we give the following:—

The artery and vein of one of the thighs having been secured by ligature, and divided beyond the ligature, the sciatic nerve was carefully dissected out from among the muscles of the thigh, and then the whole soft parts of the thigh and the bone were divided, so as to leave the limb connected with the trunk by the nerve alone. Some woorara poison was then introduced below the skin of the back, and in about three minutes affected the animal with stupefaction. It now appeared that the motor nerves of the three limbs left connected with the trunk had been paralysed, while their muscles retained their irritability; but the sensory or afferent nerves retained their power. There was thus produced the following remarkable result, viz., that pinching the skin of any part of the body (the separated limb as well), produced no reflex motions in any part excepting in the isolated limb, and in that one they were excited actively. Again by exposure of the muscles, it appeared that in all parts of the body direct stimulus called forth muscular contractions, and the heart continued to act regularly. The conclusion was then, 1st, That the motor nerves alone were affected with paralysis;

and 2nd, That the action upon them was through absorption by the blood; but 3rd, That the irritability of the muscles remained entire; and 4th, That the afferent nerves, and to a certain extent the nervous centres were not affected.

After a considerable time the reflex action ceased to be called forth, but the muscles continued irritable to direct stimulation.

II. CONIINE.

At p. 80, Kölliker states the result of six experiments made with *coniine* to be very similar to those with woorara, viz. that it acts more immediately on the motor nerves through absorption, and not upon the voluntary muscles or heart, and not upon the sensory nerves or nervous centres.

Coniine, however, operates from the stomach as well as from wounds.

III. STRYCHNINE.

At p. 81, the following results of some experiments on the action of *strychnine* are stated:—

1. Strychnine has not through the blood the slightest influence on the motor nerves.

2. Strychnine paralyses the nerves of the voluntary muscles by the over-excitation of the tetanus produced, so that the nerves are either little or not at all active.

3. On the other hand, the sensory nerves are not affected by this poison.

4. The heart is little affected by strychnine, and at the most only beats somewhat slower; but the post-lymphatic hearts at each attack of tetanus cease to act, and then go on again actively in the intervals.

5. The tetanus from strychnine may either be produced by stimuli which act upon the sensory nerves, or by excitation of the spinal marrow from the brain.

6. After strong strychnine-tetanus, the muscles are little irritable, and the rigor mortis comes on sooner than usual.

IV. OPIUM.

P. 90. *Opium* operates on frogs in a manner very similar to strychnine.

1. Opium like, strychnine, produces in frogs tetanus, which may be induced either as a reflex action, or by direct excitement from the brain.

2. This tetanus is not dependent on the presence of the brain, and Kölliker, therefore, differs from Valentin and Stannius, who assert that there is no tetanus from opium in animals deprived of the brain.

3. Opium-tetanus may also persist after removal of the medulla oblongata; but does not occur when the spinal marrow is cut below the fifth vertebra. But this is not surprising, since it has been ascertained by Harless, that the part of the spinal marrow below the fifth vertebra has no reflex action, and even in poisoning with strychnine remains inactive.

4. Opium does not operate through the blood upon the peripheral nerves. It is only when a strong solution is locally applied to the nerves that it paralyses them; but this is probably a physical action.

5. The tetanus excited by opium, interferes with the irritability of the motor nerves by over exertion (Uberanstrengung), in the same manner as strychnine.

6. Voluntary muscles affected with opium-tetanus lose their irritability soon, and rapidly become rigid.

7. The non-striated muscles, likewise, soon lose their irritability through opium.

8. The heart is less affected by opium, and was twice seen beating for six, and once for eighteen hours. Nevertheless, it is always somewhat paralysed, its action being much slower. In one instance during the tetanus, a suspension of the heart's action in diastole was observed, which, if confirmed, proves a co-operation of the medulla oblongata and excitation of the vagi.

9. The lymphatic hearts stopped during the tetanus, but recovered again in the intervals, though irregularly, and finally ceased as the spinal marrow lost its power

10. The action on the brain was not fully made out. Apparently voluntary motions were occasionally observed after the invasion of the tetanus.

11. The action on the sensory nerves also uncertain. They were obviously active so long as the tetanic spasms continued; but after these ceased, the general paralysis made it impossible to ascertain the state of the sensory nerves.

From this it appears, that opium acts, like strychnine, as a stimulant upon frogs, and at first sight this (in regard to opium) might appear to be different from its action on man and the higher animals. But it is equally true, that in them opium has a stimulant effect, and is liable to excite convulsions.

V. NICOTINE.

At p. 97, the result of six experiments on frogs with *nicotine* is described, and shows that this poison acting through the blood paralyses the motor nerves, but does not affect the muscles, the heart, or sensitive nerves. In these respects it resembles the woorara, but it differs from it in inducing tetanus, which secondarily destroys the muscular power. Also it differs in the more rapid affection of the sensorium, thus causing voluntary motions to cease long before any nervous paralysis occurs. In mammalia the results appeared different, but probably, Kölliker thinks, because of the very rapid death of the animal. Nicotine acts locally as a powerful irritant.

VI. VERATRINE.

At p. 111, the following results of seventeen experiments with veratrine, and partly with hellebore, are stated:—

1. Veratrine, is in the first place, an excitant for the medulla oblongata and spinal cord, and produces tetanus, which comes on spontaneously and by stimulation of the sensitive nerves, but lasts only a short time. After the cessation of tetanus, the reflex power is very much weakened, and soon altogether extinguished, while the conducting power of the white substance appears to be but little altered; but on this head further experiments are necessary.

2. The brain is not so directly affected, for voluntary motions still occur after tetanus has been induced. When the latter ceases, voluntary motions are abolished, but this may be from paralysis of the medulla oblongata.

3. Veratrine has no effect on the trunks of the motor nerves, the apparent loss of power in them depending upon the paralysis of the muscles.

4. The experiments are not conclusive as to the sensitive nerves; yet it seems probable that they are partially paralysed.

5. The striated muscles are very soon paralysed by veratrine. Already in the first hour they begin to lose their power, and in three hours it is quite gone. In four, they are affected with the rigor mortis. Veratrine produces the same effect upon muscles in animals which have been poisoned with woorara, and in which the nerves have thus been already paralysed; a fact which speaks strongly for the direct action on the muscles independently of the nerves.

6. The heart also is soon rendered motionless and rigid by veratrine.

7. By the direct application of a dilute solution of veratrine to the nerves, no effect is produced; but its application to the spinal cord and medulla oblongata causes tetanus, and to the muscles produces paralysis. In a more concentrated form it irritates the motor nerves, causing twitchings, and then kills.

VII. PRUSSIC ACID.

At p. 130. The results of nineteen experiments with this poison, are stated as follows:—

A series of experiments not detailed, had showed that the 4 per cent. acid of the Bavarian pharmacopœia, paralyses the sensitive nerves in a few minutes. These experiments were made by plunging one of the limbs of frogs which had been poisoned by strychnine into the prussic acid, in which case that limb was not affected with the tetanus. The heart was cut out to stop the circulation, so as not to involve the whole body by absorption.

Prussic acid also acts injuriously on the motor nerves, but very slowly.

1. Prussic acid produces paralysis in frogs first upon the brain.

2. It acts next on the spinal cord, in the first place causing reflex motions to cease, and then destroying the conducting power of the white substance.

3. The paralysis of the motor nerves comes next, and proceeds from the centre towards the periphery in the larger trunks. Whether or not the smaller nerves in the muscles are affected, seems doubtful.

4. The sensitive nerves probably lose also their conducting power.

5. The heart is paralysed, apparently from the muscular substance itself.

6. The voluntary muscles lose their power, though later than the nerves.

7. The lymphatic hearts resemble the voluntary muscles rather than the blood heart, and continue to act as long as the spinal marrow is unparalysed.

8. The muscles and hearts of frogs which have been poisoned with woorara, may afterwards be paralysed by prussic acid through the blood in a short time.

9. Prussic acid directly applied to the motor nerves, paralyses them nearly in the same time as when proceeding from the blood.

10. The sensitive nerves become rapidly insensible by the application of the prussic acid to their peripheral terminations; but the effect is local, and goes off as the acid evaporates.

11. Prussic acid paralyses the muscles locally very quickly; but in this case the rigor mortis is wanting.

12. Cyanide of potassium acts more powerfully than 1·12 per cent. (*sic*) prussic acid.

Kölliker's other experiments have shown, that in the higher animals and mammalia the operation of prussic acid is essentially the same as in frogs. The convulsions which are produced are the effect of its action upon the heart, rather than directly upon the nervous organs.

GENERAL RESULTS.

The following are the general results of the whole experiments in their physiological relation to the operation of the different poisons on the muscles, nerves, and heart, viz.:—

1. With regard to the irritability of the muscles, it deserves to be noticed—

1st, That there are some poisons, such as woorara (and probably also coniine), which, although they paralyse the nerves even within the muscles, do not in the least diminish the irritability of the muscles, nay, seem to maintain it longer than usual.

2nd, On the other hand, there are poisons, such as veratrine and probably the *extractum hellebori nigri* also, which produce no effect upon the nerves, but paralyse the muscles.

3rd. There are also poisons (such as prussic acid and its compounds) which act both on the nerves and muscles, in producing paralysis of them.

4th, Muscles, of which the nerves have been paralysed by woorara, exhibit from local irritation only local and rather tetanic contractions.

5th, Muscles which have been over-exerted from tetanic contractions produced by opium or strychnine, or electrical stimulus, are less irritable, and lose their irritability sooner than other muscles.

These experiments seem to speak strongly in favour of an independent irritability inherent in the muscular fibre. No doubt the observation of Eckhard might lead to a different conclusion. This consists in the following experiment: when a constant electrical current is passed upwards through the nerve of a muscle, the muscle is not made to contract by a weaker current of electricity through it until the first electrical circle is opened, when it immediately occurs. From this Eckhard, holding that the electric current paralyses all the nervous twigs to their extremities, but not the muscular fibres themselves, concludes that the muscular irritability depends upon the nerves. But this experiment, though in itself extremely interesting, does not prove that the constant paralysing current may not act in some passive manner upon the muscular fibre while it continues to pass through its nerves. And, on the other hand, we have all those instances in which muscular contractility is manifested without nerves, such as cilia, the substance of the lower animals, the involuntary muscular cells, &c.

In regard to the rigor mortis, these experiments appear to present something new.

1st, The invasion of the rigor mortis is quite independent of the state of the nerves in the muscles; and muscles of animals poisoned with woorara in which the nerves are fully paralysed, fall later into this state than others.

2nd, Poisons, such as veratrine and prussic acid, which paralyse the muscles themselves, occasion an earlier rigor mortis, although, with veratrine at least, the nerves of the muscles are not paralysed.

3rd, Overstraining of the muscles by tetanus, such as is induced by opium, strychnine, and electricity, causes rigor earlier.

4th, Certain substances locally applied to muscles retard the rigor (prussic acid), others hasten it (veratrine).

From this Kölliker concludes that the opinion of Stannius is untenable, according to which the rigor mortis depends upon the cessation or abolition of nervous influence in a muscle, and holds it as proved rather, that it depends on an inherent power or change in the muscle itself, probably of a molecular kind, and capable of being influenced by a variety of circumstances.

II. With reference to the action of the heart and lymphatic hearts, the following results are stated:—

1st, The paralysing poisons which act on the nerves, such as woorara and coniine, have little effect on the action of the heart, chiefly rendering its pulsations more frequent, probably from paralysis of the vagus. If the heart be cut in two, that part continues to act in which the ganglia can be proved to exist.

2nd, The poisons which paralyse the muscles paralyse also the heart, and render it soon rigid. In poisoning with prussic acid the paralysis is conjoined with great distension, with veratrine not so.

3rd, The tetanising poisons have only a small action upon the heart.

4th, The lymphatic hearts of the frog are paralysed by those poisons which paralyse the peripheral nerves, and thus do not contain the cause of their motion within themselves.

5th, In animals tetanised with strychnine and opium the lymphatic hearts are motionless, and in a contracted condition, during the attacks.

6th, The stimulation of the spinal marrow by an uninterrupted current of electricity causes a continuous contraction of these organs, which follows slower than that of the voluntary muscles.

Kölliker seems to think it most probable that the heart acts under the influence of its ganglia.

III. As respects the functions of the nervous system, the following results are stated:—

1st, The peculiar mode of action of certain poisons, as woorara, on the motor and sensory nerves (paralysing the first, but not the second, or these only a good deal later), shows that there are differences in these nerves which are not as yet capable of appreciation by any other method.

2nd, The experiments with woorara show that nerves which have been fully paralysed may regain their power afterwards.

3rd, Poisons which produce tetanus, may, by over-excitation, paralyse completely the motor nerves.

4th, Other poisons, as woorara, coniine, nicotine, and prussic acid, paralyse the motor nerves through the blood, the first three from the peripheral, the last from the central extremities.

5th, Nervous tubes with coagulated medullary sheath can still serve as perfect conductors, which seems to prove that the axis-cylinder is the alone active part.

6th, The hurtful effect of several poisons occurs more slowly when locally applied, than when they act through the blood, which appears to depend upon their difficulty of passing into the nerves.

IV. Upon the action of poisons in general the following conclusions are stated:—

1st, Different poisons exhibit particular relations to particular organs, which appear to depend on chemical affinities as yet unknown. As far as is yet known,

poisons are muscle poisons and nerve poisons. Nerve poisons appear to be divisible into three groups: 1st, such as act on the grey substance—veratrine, strychnine, and opium; 2nd, those which alter the nerve tubes—woorara, coniine; 3rd, those which affect both, as prussic acid, nicotine, and ether. And there are probably in all the groups exciting and paralysing substances. Of *purely* muscle poisons there are none; veratrine probably comes nearest to them. Blood-poisons—that is, substances which destroy the conditions of the blood elements so that the blood acts injuriously—are not known.

2nd, All poisons appear to act both through the blood and locally upon the parts which are affected by them; thus veratrine and strychnine affect the medulla in both ways, and the same is true of prussic acid, veratrine, and woorara in their relations to the muscles and the nerves. Whether this is the case for all poisons is not ascertained, and it is a matter to be recommended for the investigation of future experimenters.

3rd, The remarkable rapidity of the action of poisons is explained by the celerity of the circulation. This is best shown by the experiments made by introducing woorara and coniine into the blood of rabbits in which the sciatic nerves have been cut, and in which it is found that these nerves are already paralysed after some seconds.

In addition to the foregoing extracts translated from the German, we reprint the two following very interesting memoirs by Kölliker, from the proceedings of the Royal Society. Vol. VIII., No. 22, p. 201, and Vol. IX., No. 28, p. 72. The first communicated by Dr. Sharpey, and the second by Sir B. C. Brodie, Bart., which form a continuation of his researches on the physiological action of poisons.

I. URARI—STRYCHNIA.

The communication which I now offer to the Royal Society contains a brief statement of the results of a series of experiments which I lately made on the action of the urari poison and of strychnia on the animal economy.

1. Urari.—The urari is the well known poison from Guiana, also called Curare and Woorara. That which I employed in my experiments I owe to the liberality of my friend Professor Christison of Edinburgh. The following are the conclusions at which I arrived respecting its operation:—

1. The urari causes death very rapidly when injected into the blood or inserted into a wound; when introduced by way of the mucous membrane of the intestinal canal its effects are slow, and require a large dose for their production, especially in mammalia. When applied to the skin of frogs it is altogether inoperative.

2. Frogs poisoned with very small doses of urari may gradually recover, even after it has produced complete paralysis of the nerves. Mammalia may also be restored, even after large doses, provided respiration is maintained artificially.

3. The urari, *acting through the blood, destroys the excitability of the motor nerves.* In frogs under its operation the terminal branches of these nerves within the muscles lose their excitability in a few minutes, whilst their trunks become affected an hour or two later. If, after the nervous extremities have become paralysed, the heart of the animal be excised so as to prevent the nerves from receiving any further share of the poison, the nervous trunks may retain their excitability for three or four hours.

4. The brain is less affected by the urari than the nerves in the muscles: still when by ligature of the two aortic arches, in frogs, the poisoning is confined to the anterior half of the body, the voluntary movements of the limbs speedily cease, whilst automatic movements, of doubtful nature and probably proceeding from the medulla oblongata, may be still observed for half an hour or an hour after the poison has begun to operate.

5. The spinal cord is considerably less affected than the brain by this poison, and by local limitation of the poisoning (as in No. 4), it is found that the cord

retains its *reflex activity* from half an hour to an hour and a half, and the excitability of its white substance or its conducting power from two to three hours after the poison has taken effect. It is worthy of remark that in such cases the impaired reflex activity of the spinal cord may be revived by strychnia directly applied to it.

6. The *sensory nerves*, as shown also by locally limited poisoning, retain their functional activity as long at any rate as reflex actions can be excited, and when the depressed reflex activity has been revived by means of strychnia, these nerves are found not to have been in the slightest degree injured, so that it seems doubtful whether the urari in any way affects them.

7. *The nerves of the involuntary muscles and of the glands* are also paralysed by the action of urari, at least I find this to be true in the following cases, viz.—

a. *The pneumogastric*, as regards its influence on the heart.

b. *The sympathetic* (its cervical portion), in its relation to the iris.

c. *The nerves of the posterior lymph-hearts* of the frog.

d. *The nerves of the vessels* in the web of the frog's foot.

e. *The splanchnic nerves* of the rabbit, as affecting the peristaltic motions.

f. *The nerves governing the secretion of the submaxillary gland* in dogs.

8. *The voluntary muscles* remain perfectly excitable, but show a greater tendency than usual to merely local contractions. In general the cadaveric rigidity of these muscles appears to set in later than usual.

9. *The plain or non-striated muscles* also remain long irritable after poisoning by urari.

10. The heart, in amphibia, is little affected by urari. Its pulsation as well as the circulation of the blood goes on regularly for many hours after the poisoning is established. The only thing worthy of note is that the beat of the heart appears to be somewhat quickened, probably from paralysis of the pneumogastric nerves. In frogs poisoned with urari, the heart, when cut in two, shows the usual phenomenon, namely, that the half which contains the ganglia continues to pulsate whilst the other does not; from which it may be inferred that these ganglia are not paralysed. As to the nerves in the substance of the heart, those at least which are derived from the pneumogastric are unquestionably paralysed (vide No. 7).

11. The lymph-hearts of frogs poisoned with urari soon cease to move.

12. The blood of animals poisoned by urari is fluid and dark, but coagulates when drawn from the vessels, and forms a weak clot which is but little reddened by exposure to air. Directly mixed with blood, urari does not prevent coagulation, but the blood in this case also remains dark and scarcely reddens on exposure.

13. The blood of animals poisoned by urari has the same poisonous qualities as that substance itself, but not in a degree sufficient to produce the full effects of the poison. Urari when directly mixed with blood loses none of its efficacy.

14. Urari, in concentrated solution, applied locally to nerves, extinguishes their excitability, but only after a considerable time, and it appears to act similarly on the nerves in the substance of the muscles. Dilute solutions have no injurious operation. Applied directly to the brain and spinal cord, urari is altogether harmless provided its absorption be prevented.

15. When artificial respiration is kept up in quadrupeds poisoned with urari, I find that, as observed by Bernard, many of the secretions become increased—as the tears, saliva, urine, and mucus of the air-passages, which effect appears to be owing to the paralysis of the vascular nerves and consequent dilatation of the vessels caused by the poison.

16. In mammalia urari causes death by paralysis of the respiratory nerves and suppression of the respiration, which brings on convulsions in these animals as a collateral effect. In frogs the final extinction of the functions may also be partly ascribed to suppressed action of the lungs and defective oxidation of the blood, which at length renders the heart unfit to perform its office; but it must be observed that in this case the cause of death is not so plain, inasmuch as in these animals the functions are in a great degree independent of the pulmonary respiration.

II. Strychnia.—Some experiments with strychnia (the acetate) gave the following results:—

1. Strychnia has not the least influence on the peripheral nerves through the blood, which is best shown by cutting the nerves before administering the poison.

2. Strychnia paralyses the motor nerves of the voluntary muscles by exciting them to too energetic action, a paralysis which may be compared to that caused by powerful electric currents acting upon the nerves. In frogs, when the tetanic spasms are over, the nerves often show no trace of excitability; in mammalia they generally retain it in a slight degree, but never show the same energy of action as when uninjured.

3. Strychnia does not affect the sensory nerves.

4. The heart is not affected by strychnia, not even during the tetanic spasms, with the exception only that its pulsations are sometimes a little slower during the tetanic state. On the contrary, the lymph-hearts of frogs contract themselves as soon as the tetanus begins, and remain in this state as long as the spasms last.

5. The tetanic fits can be brought on in two ways; first, through *the sensory nerves* which, by irritating the grey substance of the spinal cord, produce the tetanic contractions as reflex movements; and, secondly, *through the brain*, which is not affected at all by strychnia, and preserves its powers of volition and sensation. Accordingly, animals poisoned with strychnia try to move in the ordinary way, but every attempt brings on a tetanic fit, so that it is plain that the spinal cord may also be excited by the brain to its peculiar actions.

6. If the tetanus produced by strychnia has been strong, the *muscles are less irritable* and pass much sooner into the state of *cadaveric rigidity*, which is very strongly marked, and seems to last longer than it generally does. The same early onset of rigidity may be observed in animals killed by tetanus excited by electricity.

II. ANTIAR.

During my stay in England, in the autumn of 1857, I was so fortunate as to acquire the rare poison of the famous *Antiaris toxicaria* (Lesch.), with which no experiments have been tried since the time of Magendie, Brodie, Horsfield, and Schnell and Emmert, (1809-1815.) I owe my specimens of the Antiar poison to my friend Professor Christison, of Edinburgh, who had it from Borneo, and to Dr. Horsfield, of London, who collected it himself during his stay at Java in the beginning of this century; and as both specimens were fully active—as some preliminary experiments made in company with my friends Dr. Sharpey and Dr. Allen Thomson showed—I thought it well worth while to devote some time to the study of the poison, and to try to elucidate its manner of action on the animal organism. The following are the principal results which I obtained in my experiments with frogs, and I hope that they will not be deemed unworthy of notice by those who take an interest in the physiological action of poisons in general.

The Antiar, like most other poisons, acts from the intestinal canal, and from wounds: but it must be remarked, that it is much more energetic and rapid when introduced into a wound. The symptoms which are observed in frogs, in the latter case, are the following:—First of all, the *voluntary movements* become less energetic, and at length cease totally, thirty to forty minutes after the introduction of the poison—after twenty-one minutes minimum, and one hour twenty-one minutes maximum. Then follows a time in which reflex movements may be caused by stimulating the skin; but this faculty also is lost very soon, viz. at from fifty to sixty minutes—at thirty-three minutes minimum, and eighty-five minutes maximum; and the animals die without the slightest trace of convulsions or tetanic spasm. If now the frogs are opened, we find that, without any exception, *the heart has ceased to beat*. The auricles are dilated, the ventricle corrugated, rather small, and generally red, as if blood had been extravasated into its muscular parietes; but very soon the exposure of the heart to the air causes the ventricle to shrink a little more, and to become pale and stiff.

as if in the state of *rigor mortis*. All interior organs, especially the lungs, liver, stomach, intestine, and kidneys, are gorged with blood, and in a state of great, especially venous, hyperæmia. The blood is fluid and rather dark, but soon coagulates when exposed to the air, and assumes a brighter colour. The lymphatic hearts cease to beat as soon as the reflex movements are lost. At the same time the nerves are yet found excitable, but their power is very low, and generally vanishes in the second hour after the application of the poison. The same must be said of the muscles, which contract very feebly when directly stimulated by galvanism, and in most cases lose their power totally in the second or third hour, and generally a little after their nerves. The *rigor mortis* begins early, sometimes in the sixth hour, and is generally well established at the eighteenth hour.

Amongst all these symptoms, to which we may add some signs of vomiting occurring now and then, there was none which attracted my attention more than the cessation of the movements of the heart, considering the great energy which this organ possesses in frogs; and I tried, therefore, before all, to elucidate the action of the Antiar upon the heart. For this purpose I instituted a new series of experiments, in which I exposed the heart by the section of the sternum, before the poison was introduced into a wound of the back; and in this way I easily got the result, that the heart ceases to beat as soon *as from the fifth to the tenth minute* after the introduction of the Antiar; and so, that first the ventricle stops, and half a minute or one minute later, also the auricles. Now, as the frogs at this time are not at all deprived of their faculty to move, we may have the rather astonishing view of an animal, with artificially-paralysed heart, which moves and leaps as freely as if nothing had happened.

The experiments just mentioned prove, *that the first action of the* Upas Antiar *is to paralyse the heart;* and I am therefore quite in accordance with Sir Benjamin Brodie, who, by his experiments on mammalia, came to the same result in 1812; whilst I cannot otherwise than disagree with Schnell (Diss. de *Upas Antiar*, Tubingæ, 1815), who assumes that this poison acts in the first place on the spinal marrow. Now this point fixed, the further question arises, whether the other symptoms mentioned, viz. the paralysis of the voluntary and reflex movements, and the loss of the irritability of the muscles and nerves, are only the results of the paralysis of the heart, or must be attributed to a specific action of the Antiar. For the elucidation of this question, I found it necessary to study the consequences of the suppression of the heart's action on the organism of frogs, which I did in the same way as it had been done by others, especially by Kunde (Müller's Archiv. 1847); viz. by cutting out the heart, or by putting a ligature around the base of it, so as to stop the circulation totally. The results of these experiments were in both cases the same, that is to say, the voluntary movements ceased in from thirty to sixty minutes, and the reflex movements after one or two hours. Hence it follows that these two symptoms of the poisoning with Antiar are simply dependent on the paralysis of the heart caused by it. With reference to the irritability of the muscles and nerves, on the contrary, it is easy to show that the ligature or excision of the heart has not the same influence as the Antiar; inasmuch as in the first case the muscles and nerves are found irritable six or seven hours, and more, after the experiment has been made. Therefore it may be said that the Antiar has a direct action on these organs.

These points once demonstrated, there remained one more question to elucidate, namely, whether the Antiar acts only upon the muscles, or also upon the nerves. If we consider that the Antiar undoubtedly paralyses the muscles, we may easily see that the loss of the excitability of the nerves possibly depends merely upon the impairment of the muscular contractility, and is therefore not real, but only apparent. With a view to determine the real state of things, I tried a third series of experiments—poisoning frogs in such a manner that the muscles of one limb were kept free from the influence of the poison. This was done in two ways: first, by putting a ligature round the crural artery and vein of one leg; and, secondly, by cutting through a leg entirely, after the ligature of its vessels, with the exception only of the ischiadic nerve. In poisoning frogs treated in

one of these ways through a wound of the back, I found that, with the exception of the heart, the Antiar acts in the first instance upon the muscles. This is shown by the fact, that in the second hour, at the time when the muscles of the poisoned parts have lost their irritability, the nerves of the sacral plexus in the abdomen still possess their full influence upon the muscles of the leg which has been kept free from the action of the poison. One might be inclined from this to conclude, that the nerves are not at all acted upon by the Antiar; but this inference would be erroneous. In fact, the experiments just mentioned, if followed a little longer, show that in the third or fourth hour the sacral plexus also becomes inactive, at a time when the muscles of the non-poisoned leg are fully contractile. The Antiar, therefore, paralyses also the nervous trunks, but later than the muscles.

From all these experiments, it seems to follow that the Antiar is a poison which acts principally upon the muscular system (the heart and the voluntary muscles) a conclusion, in favour of which I may further add, that the muscles and the heart of frogs poisoned by Urari (Woorara, Curare) lose their irritability totally, and in a short time, if Antiar is introduced into a wound some time after the Urari. If we consider that, as I have shown (see Proceedings of the Royal Society, 1856, p. 201), the Urari only acts upon the terminations of the nerves in the muscles, and does not affect the irritability of the heart and muscles at all, we may conclude, that a poison, which, as the Antiar, is capable of paralysing the muscles after the urari, has really a direct action upon the muscular fibre.

The results of my investigation into the effects of the antiar upon frogs, are therefore the following:—

1. The Antiar is a paralysing poison.
2. It acts, in the first instance, and with great rapidity (in five to ten minutes), upon the heart, and stops its action.
3. The consequences of this paralysis of the heart are the cessation of the voluntary and reflex movements in the first and second hour after the introduction of the poison.
4. The Antiar paralyses, in the second place, the voluntary muscles.
5. In the third place, it causes the loss of excitability of the great nervous trunks.
6. The heart and muscles of frogs poisoned with urari may be paralysed by Antiar.
7. From all this it may be deduced, that the Antiar principally acts upon the muscular fibre and causes paralysis of it.

So much for this time. My experiments with the Antiar upon warm-blooded animals have only begun, and I am not yet able to draw any conclusion from them. As soon as this will be possible, I shall take the liberty to submit them to the Royal Society, together with the results of my experiments with the *Upas tieuté*, which poison I had also the good fortune to obtain through the kindness of Sir Benjamin Brodie and Dr. Horsfield. With regard to the Antiar I may further add, that experiments made independently, and at the same time, by my friend Dr. Sharpey with his poison, have conducted to the same results as my own.

Printed by William Mackenzie 45 & 47 Howard Street, Glasgow